REMARKS

Before this Amendment, claims 35-39 and 70-72 were pending. By this Amendment, claims 73-79 have been added. Accordingly, claims 35-39 and 70-79 are now pending.

Claim 1 has been amended to recite that the free base is present in a therapeutically effective amount. Support for this amendment is found in the specification, at page 16, line 23.

New claim 73 recites that the free base is present in an amount of at least 3 mg. Support for this recitation is found in the specification, at page 16, line 2, and page 16, line 27.

New claim 74 recites that the free base is present in an amount of at least 6 mg. Support for this recitation is found in the specification, at page 16, line 13.

New claim 75 recites that the free base is present in an amount of more than 10 mg. Support for this recitation is found in the specification, at page 16, line 15.

New claim 76 recites that the free base is present in an amount of more than 50 mg. Support for this recitation is found in the specification, at page 16, line 15.

New claim 77 recites that the free base is present in an amount of 0.5-20 mg. Support for this recitation is found in the specification, at page 16, line 1.

New claim 78 recites that the free base is present in an amount of 3-15 mg. Support for this recitation is found in the specification, at page 16, line 8.

New claim 79 recites that the free base is present in an amount of 4-12 mg. Support for this recitation is found in the specification, at page 16, line 2.

The rejection under 35 U.S.C. §112

Claims 35-39 and 70-72 were rejected as being indefinite because, according to the Office Action, "The rejected claims are directed to a compound of formula (I), however the claims comprise limitations that describe a composition."

The Applicants continue to believe that the claims pending prior to this Amendment were not indefinite. Nevertheless, in the interests of expediting prosecution, the claims have been amended to recite "A composition comprising a compound of the following Formula I ..." rather that "A compound of the following Formula I ..."

Claim 35 has been amended to recite that the free base is present in a "therapeutically effective amount." The Applicants submit that the limitation of a "therapeutically effective amount" in amended claim 35 is not indefinite. One of ordinary skill in the art would understand the meaning of this limitation from the teachings of the specification and the prior art. This is all that is required for definiteness.[1] The specification provides extensive guidance as to what is meant by a "therapeutically effective amount." See, e.g., page 15, line 34, to page 16, line 18, where it is stated that:

> The dosing of the compounds in compliance with invention is dependent on the age, weight a status of the patient, the type of application and the interval. Generally speaking the effective daily dose lies in the 0.5-20 mg range. Typically,

[1] The test for definiteness is whether one skilled in the art would understand what is claimed when the claim is read in light of the specification and the teachings of the prior art. *See Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F. 2d 1565, 1576, 1 U.S.P.Q. 2d 1081, 1088 (Fed. Cir. 1986): "A decision on whether a claim is invalid under § 112, 2d ¶, requires a determination of whether those skilled in the art would understand what is claimed when the claim is read in light of the specification." *See also In re Moore*, 439 F. 2d 1232, 1235, 169 U.S.P.Q. 236, 238 (C.C.P.A. 1971): "[D]efiniteness of the [claim] language must be analyzed not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art."

in the case of oral administration at least 3 mg/day, for example 3-15 mg/day, preferably 4-12 mg/day is used. A typical transdermal or transmucosal daily dose, for example, for fesoterodine, for an adult patient lies, for example, at a minimum of 3 mg, preferably in the 3-15 mg range and especially preferred between 4 and 12 mg.

A pharmaceutical composition, which is suitable for once daily administration should therefore preferably contain 3-15 mg of a high purity base of the general Formula I.

For safety reasons, if the pharmaceutical composition is a transdermal formulation, it will generally be given around twice the amount of active ingredient to be administered. A typical formulation for transdermal delivery of a high purity compound of the general Formula I in compliance with the invention consequently contains at least 6 mg active ingredient, but depending on the level of dosage and the application interval, it may also contain more than 10 mg, 20 mg, 30 mg, 40 mg or 50 mg of the high purity active ingredient of the general Formula I, for example, fesoterodine, per dosing unit. If a five or even seven day application interval is scheduled the active ingredient content of an individual dosing unit may also be above 70, 80, 90 or even over 100 mg.

Prior art teachings can also be relied upon for guidance as to the meaning of a "therapeutically effective amount" because one of the compounds within the scope of claim 35 ((R)-2-[3-(1,1-diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl isobutyrate (Fesoterodine), the subject matter of claim 39) has been approved for use in the United States as the medication known as TOVIAZ®. One of ordinary skill in the art could consult the prescribing information for TOVIAZ® for guidance as to therapeutically effective amounts of the compounds of claim 35. See, e.g., Exhibit C, a copy of the prescribing information for TOVIAZ®. One of ordinary skill in the art could also consult the numerous scientific publications relating to Fesoterodine and related compounds for additional guidance.

In view of the above, it is respectfully requested that this rejection be withdrawn.

The rejection under 35 U.S.C. §102(b)

Claims 35-39 and 70-72 were rejected as being anticipated by WO 99/58478 (Meese).

According to the Office Action, Meese discloses the claimed invention at page 62, third paragraph, where "Meese et al disclose R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester (page 62, 3rd paragraph), (the compound of the instant claim 39). Meese discloses the compound as a free base" (Office Action, page 5, lines 3-5).

The Applicants respectfully traverse this rejection. The Applicants submit that the Office Action has not demonstrated that Meese disclose the free base of fesoterodine, and certainly not with a salt content of less than 10% by weight, a degree of purity of above 97 percent by weight, and in a therapeutically effective amount, as required by the present claims.

The present claims all require the free base of a compound of Formula I with a salt content of below 10 wt%. Meese does not expressly disclose a free base with such a low salt content. In particular, the portion of Meese cited in the Office Action makes no mention of salt content. Since the limitation relating to salt content is not expressly present in this portion of Meese, the Office Action must be relying on the concept of inherency to find this limitation in this portion of Meese.

To establish inherency, it must be clear that the "missing descriptive matter is necessarily present in the thing described in the reference." *In re Robertson*, 169 F. 3d 743,745, 49 U.S.P.Q. 2d 1949, 1950 (Fed. Cir. 1999) (underscoring added).

Page 62, third paragraph, of Meese has not been shown to necessarily disclose the free base of fesoterodine with a salt content of less than 10% by weight. Page 62, third paragraph, reads as follows.

> R-(+)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4 hydroxymethylphenyl ester
> Tlc: R_f 0.38 (4) , starting material: 0.26; colourless oil (yield 95%); NMR ($CDCl_3$): 19.02, 19.14, 19. 96, 20.61, 34.26, 36.92, 41.87, 43.90, 48.80, 64.84, 122.63, 122.63, 125.64, 126.19, 126.92, 127.98, 128.39, 136.96, 138,76, 143.93, 147.97, 175.39.
> Hydrochloride: colourless hygroscopic solid; $[\alpha]_D^{20} = +5.5$ (c = 1.0, chloroform) ; NMR ($CDCl_3$) : 17.03, 17.53, 18.30, 18.52, 18.95, 19.12, 31.23, 34.10, 41.69, 45.40, 54.22, 54.47, 64.00, 122.32, 126.62, 126.81, 127.40, 128.06, 128.70, 133.88, 140.64, 142.25, 147.81, 175.89.

The Office Action assumed that the compound that was subjected to TLC and produced an R_f of 0.38 was the free base of the named compound. But that is not the only interpretation, or the most likely interpretation, of the disclosure at page 62.

The disclosure on page 62 appears in a section of the Meese application beginning on page 61 that is entitled "bb) Salt formation (Example hydrochloride)". This section spans pages 61-68 and contains disclosures relating to 25 different monoamines or diamines. The first paragraph of this section (on page 61) contains a general description of how to form salts of these monoamines or diamines. Presumably this first paragraph describes what was done to each of the following 25 monoamines and diamines. This first paragraph describes the formation of hydrochloride salts of the monoamines and diamines by the use of ethereal hydrochloric acid.

> A cooled (0°C) solution of 4.94 mmol amino base in 30 ml of dry diethyl ether was treated under an atmosphere of nitrogen with 4.70 mmol (monoamines of formula II) or 9.4 mmol (diamines of formula II') ethereal (1 M) hydrochloric

> acid. The oily precipitation was washed repeatedly with dry ether and then evaporated in high vacuum. The residual product solidificated in most cases as an amorphous foam. The highly hygroscopic solids show a wide melting range above 100°C (with decomposition).
>
> The above is immediately followed by:
>
> The following compounds were prepared according to the method described above and their analytical data are listed below:

These two paragraphs describe first making the salts and then analyzing the salts that were made. This indicates that the compound that was subjected to TLC on page 62 was the hydrochloric acid salt of that compound. Thus, at least the starting material for the TLC was not the free base. The Office Action provided no evidence or argument that would explain how the TLC process described would necessarily lead to the free base of the compound named on page 62 with a salt content of less than 10% by weight.

Furthermore, there is nothing in the record to indicate that Meese, page 62, third paragraph, discloses a "therapeutically effective amount" of the free base of fesoterodine. The Applicants respectfully submit that it is not reasonable to interpret a "therapeutically effective amount" as "any amount." Such an interpretation would read the words "therapeutically effective" out of claim 35 and would thus be contrary to the well-established rule that "Claims are to be interpreted with an eye toward giving effect to all terms in the claim." *Bicon, Inc. v. Straumann Co.*, 441 F. 3d 945, 950, 78 U.S.P.Q. 2d 1267, 1272 (Fed. Cir. 2006). Interpreting a "therapeutically effective amount" as "any amount" would also be inconsistent with the many examples of "therapeutically effective amounts" disclosed in the specification at pages 15-16 (see the above discussion in connection with the indefiniteness rejection).

In view of the above, it is respectfully requested that this rejection be withdrawn.

The rejection under 35 U.S.C. §103(a)

Claims 35-39 and 70-72 were rejected as being obvious over Meese.

According to the Office Action, starting from the disclosure of Meese, conventional methods of purification could have been used to obtain the free base of fesoterodine in highly pure form and in a therapeutically effective amount. Two conventional methods of purification, TLC and column chromatography, were mentioned. See the Office Action, page 7:

> One skilled in the art would have found it obvious to prepare enough of R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester to formulate it into a dosing unit. Since Meese et al teach preparation of pharmaceutical compositions, it would be obvious to prepare enough active ingredients for a pharmaceutical preparation. Preparing sufficient quantity with the instantly claimed purity is taught by Meese. The Rf value provided by Meese on page 62, corresponds to the compounds separation on thin layer chromatography, which provides one skilled in the art with means to isolate and purify the compound of the Meese on a larger scale. Such purification can take place via column chromatography, or via Prep scale TLC, both of which are commonly utilized procedures that are well known to those skilled in the arts.

The Applicants respectfully disagree. Meese, even combined with conventional purification techniques, would not yield a therapeutically effective amount of the free base of the compound of Formula I in the recited salt and purity levels without the need for undue experimentation. The evidence of record indicates that one of ordinary skill in the art would have required undue experimentation to produce the free base at the recited salt and purity levels in a therapeutically effective amount based on Meese in combination with conventional purification techniques.

When the present inventors tried to obtain R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester (fesoterodine) having the recited degree of purity

in a therapeutically effective amount using the synthesis methods of Meese followed by conventional purification techniques, they did not succeed. The synthesis methods taught by Meese resulted in a product with a high level of contamination with reaction by-products. When conventional purification techniques were used in an attempt to purify the compound from those reaction by-products, the inventors were not successful in obtaining a pure compound in "amounts required for pharmaceutical purposes."

Meese discloses a general process for making phenolic monoesters such as fesoterodine on page 59, line 22, to page 60, line 12. The process involves reacting a carboxylic acid monochloride with (±)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol in dichloromethane and then adding triethylamine.

When this process was carried out by the present inventors with isobutyric acid chloride as the carboxylic acid monochloride and R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol, the resulting R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester (fesoterodine) was found to have a degree of purity of only 94.1% and, typically, this process gave degrees of purity that were even lower (i.e., 90.5%-94.4%). See the present application, page 42, line 27, to page 43, line 8:

> A. Manufacture of the Fesoterodine Base (B, see FIG. 1. R = i-Pr)
> Drops of a solution of 18.6 g isobutyric acid chloride in 250 ml dichloromethane were added in approximately 10 minutes to a solution of 59.8 g (175.1 mol) (R)-2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenol cooled to -3°C. (A, see FIG. 1) dissolved in 750 ml dichloromethane with agitation and cooling by ice bath. A white substance precipitated after approximately 5 minutes. For this purpose drops of a solution of 17.7 g triethylamine in 250 ml dichloromethane were added in 5 minutes under agitation and ice bath cooling. The batch was washed once with each of 250 ml water, 250 ml approximate 5% aqueous $NaHCO_3$ solution and 250 ml water. The dichloromethane extract dried

> over Na_2SO_4 was evaporated to a low small bulk on a rotary evaporator to constant weight, whereby a pale yellow, high viscosity oil was left.
> Raw yield: 63.7 g (88.5% of the theory).
> The purity of B in the HPLC in this example amounted to 94.1%. Typical range for B: 90.5% -94.4% 4 %. Decomposition occurred in the case of the high vacuum distillation trial with the formation of A and C.

The specification further states that the inventors were not able to take the impure compounds prepared according to the method of Meese and use conventional techniques to obtain purified compounds in "amounts required for pharmaceutical purposes." See the application, at page 2, line 29, to page 3, line 13:

> The bases of 3,3-diphenylpropylamines published in WO 99/58478 [Meese] are manufactured by 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol being converted under alkaline conditions with an appropriate acid chloride, for example, isobutyric acid chloride (see Example Execution 3aa of WO 99/58478).
>
> This reaction, however, only leads disadvantageously to approximately 90% up to a maximum approximate 94% of the desired main product (B). The product consistently contains 6-10% impurities of the starting substance (A), the used acylation agent as well as undesired reaction products in the form of the corresponding di-ester of the acylating reagent used (C) of the monoester (D) of the 4-hydroxy group (see FIG. 1) as well as by dimerization/polymerization.
>
> Attempts by the inventor of this patent application to make the synthesis reaction more selective by, for example, varying the amount of the acylating reagent and/or the acylating conditions (temperature, solvent, concentrations, sequence of the addition, among other things), did not lead to the desired result.
>
> Even extensive trials to purify the high purity base from the product mix in the amounts required for pharmaceutical purposes using conventional procedures remained unsuccessful.

Enclosed is a Declaration of Ralf Kanzler under 37 C.F.R. §1.132 (Kanzler Declaration), submitted in connection with U.S. Patent Application Serial No. 12/141,489, a divisional application of the present application. The Kanzler Declaration describes numerous attempts that were made to purify fesoterodine free base by three commonly used purification techniques:

chromatography, re-crystallization, and distillation. All three techniques failed to yield purified fesoterodine base.

Thus, actual experimental work, reported both in the present specification and in the Kanzler Declaration, supports the Applicants' argument that Meese, even combined with conventional purification techniques, would not yield a therapeutically effective amount of the free base of the compound of Formula I in the recited purity level without the need for undue experimentation.

Moreover, Meese itself casts doubt on the ability of conventional purification techniques such as TLC to provide compounds within the scope of the present claims with the recited degree of purity in a therapeutically effective amount.

Page 62, third paragraph, of Meese discloses the results of TLC on R-(+)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4 hydroxymethylphenyl ester. The R_f of this compound is listed as "R_f 0.38 (4)." The number 4 in parentheses appears to refer to the solvent system that was used in the TLC. Page 37 of Meese describes the TLC solvent systems used by Meese.

> Thin-layer chromatography (tlc, R_f values reported) was conducted on precoated 5x10 cm E. Merck silica gel plates (60F254), spots were visualized by fluorescence -quenching or spraying with alkaline potassium permanganate solution. Solvent systems: (1), ethyl acetate/n-hexane (30/70, v/v-%);(2), toluene/acetone/methanol/acetic acid (70/5/20/5, v/v-%); (3), n-hexane/acetone/diethylamine (70/20/10, v/v-%); (4), n-hexane/acetone/triethylamine (70/20/10, v/v-%); (5), ethyl acetate/n-hexane/2-propanol/triethylamine (60/40/20/1, v/v-%); (6), ethyl acetate/triethylamine (90/10, v/v-%); (7), cyclohexane/acetone/acetic acid (80/20/0.5, v/v-%).

It appears that the compound of page 62, third paragraph, of Meese was subjected to TLC using solvent system (4), a solvent system of n-hexane/acetone/triethylamine (70/20/10, v/v-%), and produced an R_f of 0.38. At the paragraph bridging pages 67 and 68, Meese discloses that the compound (±)-Malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester also produced an R_f of 0.38 in TLC solvent system (4).

In other words, Meese discloses that two compounds with related, but different structures, gave the same R_f value when subjected to TLC in the same solvent system. This conventional purification technique was incapable of separating these two compounds. The compounds of Formula I and their reaction by-products are also compounds with related, but different structures. The evidence provided by Meese thus indicates that TLC would also be unable to separate compounds of Formula I from their reaction by-products. At the very least, the evidence indicates that separating the compounds of Formula I from their reaction by-products would not be routine but instead would require a great deal, i.e., an undue amount, of experimentation.

There are other instances where Meese shows that the conventional purification technique of TLC was unable to separate compounds with related, but different structures, where one of the compounds was within the scope of the present claims. Page 62, lines 8-12, of Meese show the results of TLC of (±)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester in solvent system (4). This compound is within the scope of present claim 35 and is specifically recited in claim 37.[2] Its R_f value is given as: "R_f 0.43 (4)." At the

[2] "2-[3-(1,1-diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl isobutyrate," recited in claim 37, specifies the same chemical structure as "(±)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester," disclosed in Meese, at page 62, lines 8-12.

paragraph bridging pages 61 and 62, Meese discloses that the compound (±)-n-Butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester also produced an R_f 0.43 in TLC solvent system (4).

Again, Meese discloses that two compounds, related in structure, one of which is within the scope of the present claims, could not be separated by TLC. The compounds of Formula I and their reaction by-products are also compounds with related, but different structures. The evidence provided by Meese thus indicates that TLC would also be unable to separate compounds of Formula I from their reaction by-products. At the very least, the evidence indicates that separating the compounds of Formula I from their reaction by-products would not be routine but instead would require undue experimentation.

Moreover, two other compounds in the relevant section of Meese (the section entitled "bb) Salt formation (Example hydrochloride)" at pages 61-68) also are said to have R_f values of 0.43. See the disclosure on page 68 pertaining to the compounds (±)-Pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester and (±)-Hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester. Although the solvent systems used for these two compounds are not specified, it can be noted that, of the 22 solvent systems that are specified in this section of Meese, 21 are solvent system (4). Thus, it can be inferred with a reasonable likelihood that these two compounds, which have structures somewhat similar to the structures of the compounds recited in the present claims, also gave the same R_f value in the same solvent system as (±)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, a compound within the scope of the present claims

Clearly, the evidence of record indicates that the convention purification technique of TLC would not appear to be able to easily separate the compounds of Formula I from their reaction by-products.

It is well settled that prior art references cannot make obvious claimed subject matter unless those prior art references enable the claimed subject matter. "References relied upon to support a rejection under 35 U.S.C. 103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public. ... An invention is not 'possessed' absent some known or obvious way to make it." *In re Payne*, 606 F. 2d 303, 314, 203 U.S.P.Q. 245, 255 (C.C.P.A. 1979) (citation omitted). Moreover, enablement requires a method of obtaining the claimed subject matter without undue experimentation. "Enablement is not precluded by the necessity for some experimentation ... However, experimentation needed to practice the invention must not be undue experimentation." *In re Wands*, 858 F. 2d 731, 733, 8 U.S.P.Q. 2d 1400, 1404 (Fed. Cir. 1988).

Thus, the evidence of record indicates that Meese in combination with conventional purification techniques does not enable the production of free bases of the compounds of Formula I having the degree of purity recited in the present claims in therapeutically effective amounts since Meese in combination with conventional purification techniques does not provide a method of obtaining compounds of Formula I having the degree of purity recited in the present claims in therapeutically effective amounts without undue experimentation.

Since what is being claimed in the present application requires compounds having a specified salt content and degree of purity, in therapeutically effective amounts, Meese, even in

combination with conventional purification techniques, cannot make obvious claims reciting such compounds unless Meese in combination with conventional purification techniques enables the production of such compounds. As seen from the inventors' experiments, the Kanzler Declaration, and the disclosures of Meese itself, Meese, even in combination with conventional purification techniques, does not enable the production of such compounds.

By failing to enable the presently claimed subject matter, including its limitations with respect to salt content, purity, and therapeutically effective amount, Meese, even in combination with conventional purification techniques, cannot support this obviousness rejection.

In view of the above, it is respectfully requested that this rejection be withdrawn.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with the filing of this paper, or any defect seen to be remaining in this application after the filing of this paper. The Director is authorized to charge Kenyon & Kenyon's Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully Submitted,

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BY: /Joseph A. Coppola/
Joseph A. Coppola
Reg. No. 38,413
KENYON & KENYON LLP
One Broadway
New York, NY 10004
(212) 425-7200 (telephone)
(212) 425-5288 (facsimile)

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